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Lipoprotein(a) in nephrotic syndrome

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Lipoprotein(a) in nephrotic syndrome. Lipoprotein(a) [Lp(a)] is an independent risk factor for cardiovascular disease, and it has also been speculated that it promotes thrombosis. Recent studies have shown that patients with gross proteinuria have greatly increased plasma levels of Lp(a), but the genesis is obscure. In the present study, plasma Lp(a) levels were measured in 31 patients with nephrotic syndrome (NS), 24 patients with IgA nephropathy and 43 healthy control subjects. Lp(a) levels were significantly elevated in NS (median 49.0 mg/dl), in contrast to the control subjects and patients with IgA nephropathy (median 7.0 and 9.7 mg/dl, respectively). Plasma Lp(a) levels fell markedly in 10 of 10 NS patients after remission. In NS, Lp(a) levels correlated directly with serum cholesterol levels ($P < 0.05$) and indirectly with plasma orosomucoid levels ($P < 0.05$), but not with serum albumin, triglycerides, HDL cholesterol, urinary protein excretion or GFR. In addition, Lp(a) tended to be higher in NS patients with edema (median 54.3 mg/dl) than in patients without edema (19.0 mg/dl; $P = 0.06$). Nine NS patients were further evaluated with plasma ANP levels and urinary sodium excretion. Plasma Lp(a) correlated directly with ANP ($P < 0.01$) and indirectly with urinary sodium excretion ($P < 0.05$). Excellent correlations were found between Lp(a) and VLDL cholesterol and VLDL triglycerides, respectively, suggesting a close link between Lp(a) and triglyceride-rich lipoproteins in nephrosis.

Hyperlipidemia is a common feature of nephrotic syndrome (NS) and is often included in the definition of the condition [1]. Both increased synthesis and decreased clearance of lipoproteins may contribute to the hyperlipidemia usually characterized by increases in the total and low-density lipoprotein (LDL) cholesterol levels, with normal or reduced high-density lipoprotein (HDL) cholesterol [2]. In non-nephrotic patients this type of lipid abnormality is associated with accelerated atherosclerosis [3]. Furthermore, a considerably increased incidence of coronary heart disease has been reported in patients with NS [4, 5].

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein, originally described by Berg [6], consisting of a particle similar to low-density lipoprotein (LDL), with apoprotein (a) covalently linked to apoprotein B-100 by a disulphide bridge [7]. Plasma apo(a) levels vary several hundred-fold in the population, and an inverse relation between the molecular size of apo(a) and its plasma levels has been found [7]. Moreover, recent studies have demonstrated that a major part (≈90%) of the interindividual variability is due to genetic factors [8]. In normal subjects the plasma Lp(a) correlates to the rate of Lp(a) synthesis rather than to the rate of catabolism [9]. Increased concentrations of Lp(a) (>30 mg/dl) are associated with an increased risk of coronary artery disease, similar to and synergistic with increased LDL cholesterol levels [10, 11]. It has also been proposed that Lp(a) may act as a competitive inhibitor of plasminogen activation and thus promote thrombosis rather than fibrinolysis [12–14]. Due to the strong genetic impact, intraindividual plasma Lp(a) levels are stable. Hitherto only a few clinical conditions have been found to significantly affect plasma Lp(a) concentrations [15]. It is noteworthy that increased levels of Lp(a) have recently been described in patients with NS [16–19], but the genesis of this lipid abnormality remains obscure.

The aim of the present study was to study plasma Lp(a) levels and their relationship with serum lipid and lipoprotein levels in patients with NS. In addition we measured 24-hour urinary protein excretion (UPE), glomerular filtration rate (GFR), mean arterial blood pressure, plasma orosomucoid and serum albumin in the same 31 patients with NS. The presence or absence of clinically overt edema was also determined. Nine patients with NS of recent onset were further investigated with respect to urinary sodium excretion and plasma ANP levels. Furthermore, Lp(a) levels were followed in 10 patients during remission of NS. A matched group of 24 patients having IgA nephropathy with only minor urinary protein losses, as well as 10 healthy subjects, served as controls.

Methods

Patients with nephrotic syndrome

A total of 31 adult patients (18 men and 13 women) with NS seen at the Renal Clinic, Huddinge University Hospital, were enrolled in the study. Their ethnic origin was Caucasian in 30 cases and Asian in one case. NS was defined as UPE >3.0 g/24 hours and serum albumin ≤30 g/liter in the presence or absence of clinically overt edema. Patients with systemic diseases like diabetes mellitus, rheumatoid arthritis and SLE or massive obesity (body mass index >34 kg/m^2) were excluded. The median duration of the NS was eight months (range 1 to 240 months) at the time of examination. Sixteen patients were taking diuretic agents at the time of examination. Five patients were on ACE inhibitors, three on beta blockers, two on calcium antagonists, and two patients were taking lipid-lowering drugs

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Table 1. Histological diagnosis from renal needle biopsy and Lp(a) concentration in plasma of 31 patients with nephrotic syndrome

Renal pathology	*N*	Lp(a) *mg/dl*
Membranous GN	13	39.7 (20.0–98.7)[a]
Focal segmental sclerosis	5	40.1 (36.4–63.9)[a]
IgA nephropathy	3	14, 14, 59
Mesangiocapillary GN	3	18, 38, 50
Minimal change GN	3	49, 83, 97
Amyloidosis	2	6 and 78
Mesangioproliferative GN	1	74
Single kidney (not biopsied)	1	41
Total	31	49.0 (19.4–79.0

[a] Values represent median and quartiles

(simvastatin and gemfibrozil, respectively) at the time of investigation. Nine patients were on no regular medication. The presence or absence of clinically overt peripheral edema was determined at a routine physical examination in all patients. A renal biopsy had been performed in all except one patient with a single kidney; Table 1 lists the patients grouped according to morphological findings. Remission (complete or partial) of the NS, defined as a decrease in UPE <3 g/24 hr and an increase in serum albumin >30 g/liter, occurred in 10 patients during the follow-up (Table 2). In these patients the plasma Lp(a) levels were reassessed.

All newly diagnosed patients with NS ($N = 10$) of fairly recent (median 7 months; range 1 to 24 months) onset, admitted to the Renal Clinic at Huddinge University Hospital during the study period, were asked to participate in further examinations. These included the plasma lipid profile, plasma ANP, urinary sodium excretion and GFR. The nine patients who agreed to participate formed a subgroup of patients with NS (NS_{sg}). All drugs (diuretics only) were discontinued at least 48 hours prior to the investigation. The clinical and laboratory characteristics of these nine patients are presented in Table 3.

Patients with IgA nephropathy

Twenty-four patients having a biopsy-proven IgA nephropathy with UPE <2.5 g/24 hr were studied. The group was selected to match the nephrotic group with respect to age, body mass index, GFR and mean blood pressure (Table 4). Twelve patients were taking ACE inhibitors, six patients beta blockers, five patients diuretics and one patient a calcium antagonist. No patient was on lipid-lowering drugs, and six patients were not taking any medication regularly.

Healthy control subjects

Plasma Lp(a) levels were analyzed in a total of 43 healthy control subjects (C_{tot}), none of whom was on any medication. A subgroup of 10 control subjects (C_{sg}) participated in the same additional examinations as NS_{sg}.

All patients gave their informed consent and the study was approved by the Ethics Committee at Huddinge University Hospital.

Protocol

Throughout the study, patients or control subjects were not subjected to any dietary restrictions. Blood samples for determinations of cholesterol, triglyceride, HDL-cholesterol, Apo A_1, Apo B, Lp(a), serum albumin and plasma orosomucoid were drawn from all patients and controls (C_{sg}) after they had fasted overnight. A determination of plasma orosomucoid was missing in two NS patients. A more detailed lipoprotein analysis was performed, as detailed below, in eight NS patients. The UPE was determined in all patients with NS and IgA nephropathy, whereas a dipstick test was used to exclude proteinuria in the controls. In the nephrotic group, GFR was determined with inulin ($N = 9$), ^{51}Cr-EDTA ($N = 17$) or 24-hour creatinine clearance ($N = 4$), whereas a clearance determination was missing in one patient. In the IgA nephropathy group ($N = 24$) GFR was estimated with ^{51}Cr-EDTA clearance, whereas inulin clearance was used to estimate GFR in the control group.

Measurements of blood lipids and lipoproteins

The levels of serum cholesterol and triglycerides levels were analyzed by standard enzymatic procedures (Boehringer Mannheim, Mannheim, Germany). HDL-cholesterol levels were determined after precipitation of apo B-containing lipoproteins by phosphotungstic acid [20]. LDL-cholesterol levels were calculated using Friedewald's formula [21]. In eight cases a more detailed lipoprotein analysis was performed using a combination of ultracentrifugation and precipitation [22]. Serum samples (4 ml) were spun at 35,000 rpm for 18 hours at 4°C in a Centrikon T-2060 ultracentrifuge (Contron Roche, Zürich, Switzerland) equipped with a 45.6 rotor. The tubes were sliced and the floating fraction as well as the infranatant were analyzed for cholesterol and triglyceride contents. A portion of the infranatant was treated with phosphotungstic acid to precipitate apo B-containing lipoproteins. Apolipoproteins A_1 and B were determined using an immunonephelometric procedure (Behring AG, Marburg, Germany). Lp(a) levels were analyzed using a commercially available, two-site immunoradiometric assay (Pharmacia, Uppsala, Sweden). The method uses two monoclonal antibodies to different epitopes of apo(a), one labeled with ^{125}I and one coupled to microsepharose. The coefficient of variation was 3.8% at a standard concentration of 36.4 mg/dl and 7.2% at a standard concentration of 13.7 mg/dl. The Lp(a) serum standard was obtained from Immuno AG (Vienna, Austria).

Other laboratory procedures

The methods of inulin and ^{51}Cr-EDTA clearance were applied as previously described [23]. Plasma ANP was analyzed by radioimmunoassay (Milab, Malmö, Sweden) [24]. Plasma orosomucoid levels were measured by a standard immunonephelometric procedure (Behring AG). Determinations of serum albumin, the UPE and urine sodium were carried out in the Department of Clinical Chemistry, Huddinge Hospital, using routine methods.

Calculations and statistical analysis

The mean arterial pressure (MAP) was calculated as diastolic BP + one-third of pulse pressure. The body mass index was calculated as weight (kg)/height $(m)^2$. The distribution of Lp(a) was not normally distributed and Lp(a) was therefore given as medians and quartiles. Also, the duration of NS was not normally distributed and was therefore given as median and range. Differences between the groups were assessed using the two sample non-parametric Mann-Whitney U-test. The

Table 2. Renal pathology and laboratory characteristics of 10 patients with remission of nephrotic syndrome

No.	Renal pathology	UPE *g/24 hr*		Serum albumin *g/liter*		Lp(a) *mg/dl*	
		NS	Rem.	NS	Rem.	NS	Rem.
1	Membranous GN	5.2	2.9	25	32	24	11
2	IgA nephropathy	3.8	<0.1	24	38	14	2
3	Focal segmental sclerosis	14	0.9	15	32	59	30
4	Membranous GN	10.4	2.8	19	37	20	7
5	IgA nephropathy	3.6	1.0	21	41	59	40
6	Membranous GN	5.4	<0.1	25	35	178	110
7	Minimal change GN	13.9	<0.1	13	35	97	17
8	Membranous GN	3.5	1.5	14	38	128	32
9	Minimal change GN	11.9	0.4	14	38	83	63
10	Minimal change GN	10.1	<0.1	8	36	49	10

Abbreviations are: GN, glomerulonephritis; UPE, urinary protein excretion; NS, nephrotic syndrome; Rem., remission.

Table 3. Clinical characteristics in 9 patients with nephrotic syndrome further evaluated with plasma ANP levels and urinary sodium excretion as compared to 10 controls

No.	Sex (M/F)	Renal pathology	Edema	Duration *months*	Medication	Length of treatment	Lp(a) *mg/dl*	ANP *pmol/liter*	U_{Na} *mmol/hr*	GFR *ml/min*
Nephrotic syndrome										
1	M	IgA nephropathy	Neg.	8	0	0	14	4	17.1	70
2	M	Membranous GN	Neg.	8	0	0	12	10	23.4	78
3	M	Membranous GN	Pos.	24	0	0	49	17	10.3	39
4	F	Mesangioproliferative GN	Pos.	7	Furosemide	2 months	74	10	2.4	82
5	F	Membranoproliferative GN	Pos.	19	Furosemide	7 months	38	20	2.3	49
6	M	Membranous GN	Pos.	5	Furosemide	5 months	172	41	2.5	60
7	M	Membranous GN	Pos.	1	Amiloride	2 weeks	128	28	4.3	65
8	M	Amyloidosis	Pos.	1	0	0	78	19	2.7	70
9	M	Minimal change GN	Pos.	2	0	0	97	18	5.7	95
Mean ± SEM				7 (1–24)[d]			74.0 (32.0–104.8)[ac]	19 ± 4	7.9 ± 2.5	68 ± 6[b]
Controls										
N = 10	M		Neg.		None		7.0 (2.5–30.8)[c]	11 ± 2	13.1 ± 1.5	110 ± 3

[a] $P < 0.01$ and [b] $P < 0.001$ vs. controls
[c] Values represent median and quartiles
[d] Values represent median and range
Abbreviations are: ANP, atrial natriuretic peptide; U_{Na}, urinary sodium excretion; GFR, glomerular filtration rate; GN, glomerulonephritis.

Wilcoxon signed-rank test was used to test changes in plasma levels of Lp(a) following remission of NS. The Wald-Wolfowitz run-test was used to test differences in the cumulative frequencies of plasma Lp(a) and serum cholesterol, respectively, in NS, IgA nephropathy and C_{tot} groups and also to test differences in the cumulative frequency of Lp(a) in NS patients with or without edema. Linear regression analysis was used to correlate the various parameters shown in Table 6. All data except Lp(a) are given as means ± SEM. A two-tailed *P* value less than 0.05 was considered to be statistically significant.

Results

Basal clinical data and blood lipids

Basal laboratory data in NS and IgA nephropathy and C_{sg} groups are shown in Table 4. The lipid profiles in the three groups are shown in Table 5. As can be seen the median plasma level of Lp(a) (49.0 mg/dl; quartiles 19.4 to 79.0 mg/dl) in NS patients was significantly higher than in patients with IgA nephropathy (median 9.7; quartiles 4.8 to 17.0 mg/dl), C_{tot} (median 7.0; quartiles 2.8 to 26.8 mg/dl) and C_{sg} (median 7.0; quartiles 2.5 to 30.8 mg/dl), respectively. There was no evidence of sex-related differences in the Lp(a) concentration, as

Table 4. Some basal clinical and laboratory findings in Controls (C_{sg}) and patients with IgA nephropathy or nephrotic syndrome

	Controls (*N* = 10)	IgA nephropathy (*N* = 24)	Nephrotic syndrome (*N* = 31)
Age *years*	33 ± 1	42 ± 2[a]	45 ± 2[b]
Body mass index kg/m^2	24 ± 1	25 ± 1	25 ± 1
Glomerular filtration rate *ml/min*	110 ± 3	67 ± 5[c]	67 ± 6[c]
Urinary protein excretion *g/24 hr*	<0.3 g/liter	1.3 ± 0.1	8.8 ± 0.7[d]
Serum albumin *g/liter*	38 ± 1	37 ± 1	19 ± 1[c,d]
Mean arterial pressure *mm Hg*	86 ± 2	102 ± 2[c]	102 ± 2[c]

[a] $P < 0.05$, [b] $P < 0.01$ and [c] $P < 0.001$ vs. controls
[d] $P < 0.001$ vs. IgA nephropathy

the median plasma Lp(a) level was 49.0 mg/dl (quartiles 15.1 to 81.8 mg/dl) in the nephrotic men (*N* = 18) compared to a median plasma Lp(a) level of 47.7 mg/dl (quartiles 40.6 to 66.0 mg/dl) in the nephrotic women (*N* = 13). The cumulative frequencies of Lp(a) in the NS, IgA nephropathy and C_{tot} groups are shown in Figure 1. Significant differences in the cumulative frequencies

Table 5. Mean lipid and apolipoprotein concentrations in the study groups

	Controls (N = 10)	IgA nephropathy (N = 24)	Nephrotic syndrome (N = 31)
S-cholesterol *mmol/liter*	4.9 ± 0.2	6.9 ± 0.3[c]	10.1 ± 0.5[c,e]
S-triglycerides *mmol/liter*	1.0 ± 0.05	2.0 ± 0.2[c]	2.8 ± 0.3[c,d]
HDL-Cholesterol *mmol/liter*	1.3 ± 0.05	1.0 ± 0.06[b]	1.5 ± 0.1[e]
LDL/HDL ratio	2.6 ± 0.2	5.6 ± 0.5[c]	5.6 ± 0.5[c]
Apo A_1 *g/liter*	1.26 ± 0.06	1.46 ± 0.05[a]	1.64 ± 0.08[a]
Apo B *g/liter*	0.91 ± 0.06	1.45 ± 0.08[c]	2.40 ± 0.15[c,e]
Lp(a) *mg/dl*	7.0 (2.5–30.8)[f]	9.7 (4.8–17.0)[f]	49.0 (19.4–79.0)[b,e,f]

[a] $P < 0.05$, [b] $P < 0.01$ and [c] $P < 0.001$ vs. controls
[d] $P < 0.05$ and [e] $P < 0.001$ vs. IgA nephropathy
[f] Values represent median and quartiles

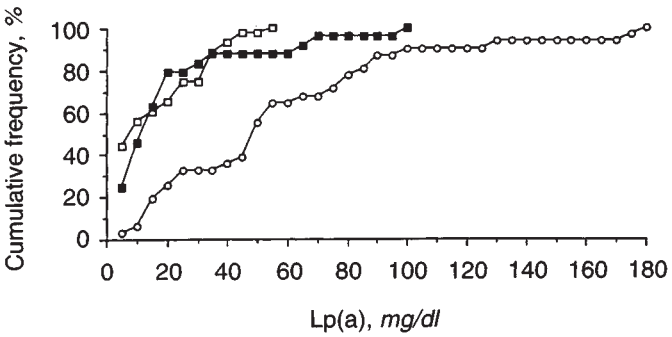

Fig. 1. *Cumulative frequency distribution curves of plasma Lp(a) concentrations in patients with nephrotic syndrome (○), IgA nephropathy (■) and 43 control subjects (C_{tot}) (□).* Significant changes were found with the Wald-Wolfowitz run-test between patients with nephrotic syndrome and IgA nephropathy ($P < 0.05$) and control subjects ($P < 0.01$), respectively.

of Lp(a) were seen between NS patients and both IgA nephropathy patients ($P < 0.05$) and C_{tot} ($P < 0.01$). Plasma orosomucoid, measured in NS patients and C_{sg} only, were significantly decreased ($P < 0.01$) in NS (0.59 ± 0.04 g/liter; $P < 0.01$) as compared to the 10 healthy subjects (0.71 ± 0.05 g/liter). A significant positive correlation was found between serum albumin and plasma orosomucoid ($r = 0.44$; $P < 0.05$) in the NS group.

No significant difference in Lp(a) levels, with respect to the underlying renal pathology was seen in the NS group (Table 1). All correlations obtained between the blood lipids and the other parameters evaluated in the NS group are presented in Table 6. Lp(a) levels correlated directly with serum cholesterol ($r = 0.38$; $P < 0.05$) and indirectly with plasma orosomucoid levels ($r = -0.39$; $P < 0.05$). It is noteworthy that no correlations were found between Lp(a) and any of the other parameters. However, the concept that plasma Lp(a) levels may be mostly influenced by hepatic synthesis prompted us to compare VLDL and Lp(a) levels in nephrosis. In a subgroup of patients ($N = 8$) a more detailed lipoprotein analysis was undertaken. In this group, Lp(a) correlated significantly with VLDL-cholesterol ($r = 0.92$; $P < 0.01$) and with VLDL-triglycerides ($r = 0.92$; $P < 0.01$; Fig. 2).

Lp(a) following remission of the nephrotic syndrome

Ten NS patients had a complete or partial remission of their disease, following a mean period of 9 ± 2 months. Treatment with corticosteroids had preceded the remission in five of the cases. After remission edema disappeared, serum albumin increased from 18 ± 2 to 36 ± 1 g/liter, and the median plasma Lp(a) level fell from 59.0 mg/dl (quartiles 24.0 to 97.0 mg/dl) to 23.5 mg/dl (quartiles 10.0 to 40.0 mg/dl; $P < 0.01$). Individual changes in serum albumin and plasma Lp(a) levels are depicted in Table 2 and Figure 3.

Lp(a), edema and ANP

Serum albumin was lower (17 ± 1 g/liter; $P < 0.01$) in 22 patients with NS and peripheral edema than in nine patients without any clinical signs of edema (24 ± 1 g/liter). Lower plasma orosomucoid levels were observed (0.47 ± 0.05 g/liter) in 20 patients with NS and peripheral edema than in nine NS patients without any clinical signs of edema (0.71 ± 0.08 g/liter; $P < 0.01$). The median plasma Lp(a) level tended to be higher in the NS group with edema (54.3 mg/dl; quartiles 38.2 to 82.6 mg/dl) than in the nine NS patients without clinical edema (19.0 mg/dl; quartiles 14.2 to 49.7 mg/dl), although the difference did not attain statistical significance ($P = 0.06$; Fig. 4). No significant differences between NS patients with or without edema were observed in mean serum levels of cholesterol or UPE. The cumulative frequency of serum cholesterol was similar ($P = 0.90$) in NS patients with or without edema (Fig. 4). A tendency to higher ANP levels was observed in the NS_{sg} group, as compared to the C_{sg} group (19 ± 4 vs. 11 ± 2 pmol/liter; $P = 0.07$). The urinary sodium excretion was 7.9 ± 2.5 mmol/hr in the NS_{sg} as compared to 13.1 ± 1.5 mmol/hr in C_{sg} ($P = 0.09$). In NS_{sg}, significant correlations were found between Lp(a) and ANP ($r = 0.88$; $P < 0.01$) and urinary sodium excretion ($r = -0.67$; $P < 0.05$), respectively (Fig. 5). Multiple regression analysis confirmed that higher ANP concentrations were associated with higher Lp(a) levels, independently of the serum albumin concentrations and the presence or absence of clinical edema. However, in view of the genetic impact on Lp(a) isoforms and plasma levels, these findings in a limited group of patients will have to be interpreted with caution. No correlations were found in NS_{sg} between plasma ANP levels or urinary sodium excretion and cholesterol, triglycerides, HDL-cholesterol, Apo A_1 and Apo B levels.

Discussion

The present study showed that patients with NS of diverse etiologies had a significantly higher plasma concentration of Lp(a) lipoprotein than both a matched group of IgA nephropathy patients with less pronounced proteinuria and a group of healthy control subjects. The present results thus confirm previous studies which have demonstrated a major increase in plasma Lp(a) levels in the nephrotic state [16–19].

The physiologic role and metabolism of Lp(a) is not clear. The plasma levels of Lp(a) are under the control of the apo(a) gene to a large extent [7, 8] and are largely unaffected by age, sex and prandial status [25]. However, the hepatic synthesis rate appears to be of importance [26] and hormones have been found to influence Lp(a) levels [27–30]. Based on several

Table 6. Correlations between lipids and apolipoproteins and GFR, plasma orosomucoid, serum albumin and UPE in 31 patients with nephrotic syndrome

	Serum cholesterol	Serum triglycerides	Lp(a)	HDL cholesterol	Apo A_1	Apo B
	mmol/liter		*mg/dl*	*mmol/liter*	*g/liter*	
Serum triglycerides *mmol/liter*	NS					
Lp(a) *mg/dl*	$r = 0.38^a$	NS				
HDL cholesterol *mmol/liter*	NS	$r = -0.53^b$	NS			
Apo A_1 *g/liter*	NS	$r = -0.48^b$	NS	$r = 0.89^c$		
Apo B *g/liter*	$r = 0.84^c$	$r = 0.36^a$	NS	NS	NS	
Glomerular filtration rate *ml/min*	NS	$r = -0.46^a$	NS	$r = 0.41^a$	NS	NS
Plasma orosomucoid *g/liter*	$r = -0.51^b$	NS	$r = -0.39^a$	NS	NS	NS
Serum albumin *g/liter*	$r = -0.45^a$	NS	NS	NS	NS	$r = -0.45^b$
Urinary protein excretion *g/24 hr*	NS	NS	NS	$r = -0.51^b$	$r = -0.45^a$	NS

[a] $P < 0.05$, [b] $P < 0.01$ and [c] $P < 0.001$

Abbreviations are: GFR, glomerular filtration rate; UPE, urinary protein excretion; NS, not significant.

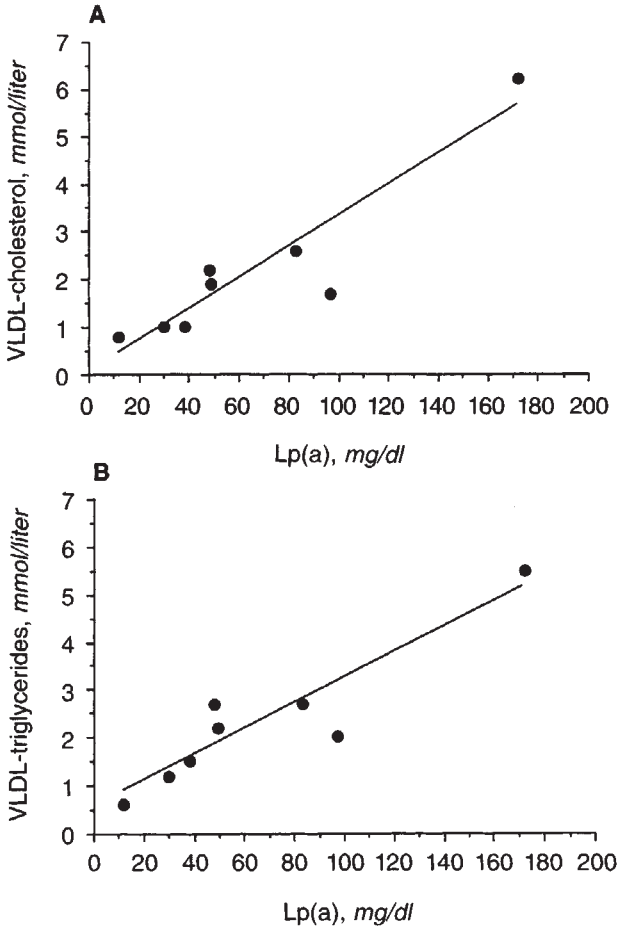

Fig. 2. *Correlations between plasma Lp(a) and VLDL-cholesterol (r = 0.92; P < 0.01) and VLDL-triglycerides (r = 0.92; P < 0.01) in 8 patients with nephrotic syndrome.*

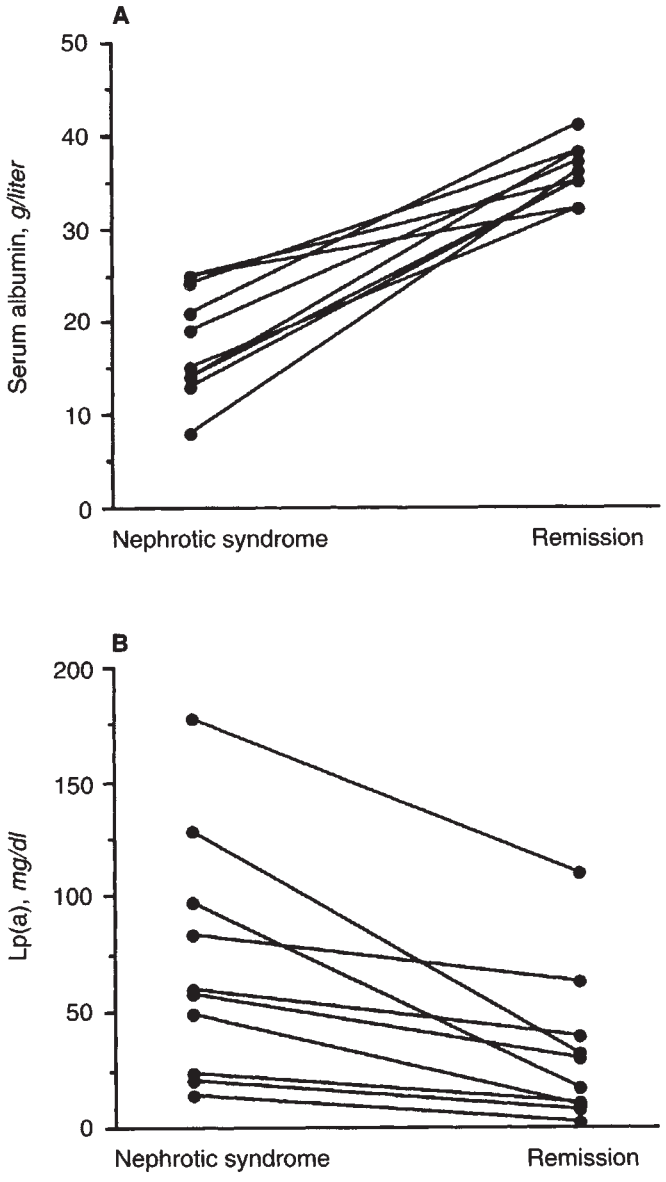

Fig. 3. *Individual changes in serum albumin and plasma Lp(a) levels in 10 patients with remission of nephrotic syndrome.*

studies, plasma Lp(a) levels above 30 mg/dl have been considered an independent risk factor for the development of cardiovascular disease in the general population [31, 32]. In the present study ≈70% of the nephrotic patients had plasma Lp(a) levels above 30 mg/dl, as compared to only ≈20% of the

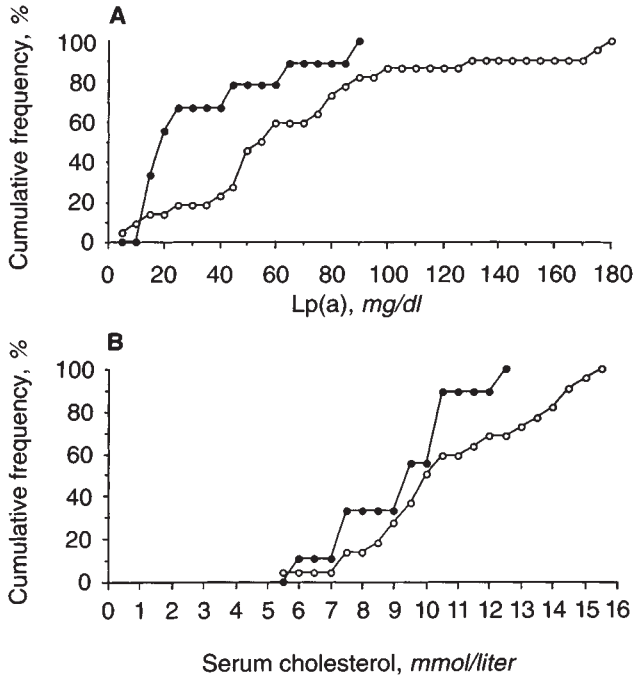

Fig. 4. *Cumulative frequency distribution curves of plasma Lp(a) and serum cholesterol concentrations in nephrotic patients with (○) and without (●) peripheral edema.* With the Wald-Wolfowitz run-test a *P* value of 0.06 was found when testing for Lp(a) in the 2 subgroups of nephrotic patients while a *P* value of 0.90 was found when testing the cumulative frequency distribution for serum cholesterol in the 2 subgroups of nephrotic patients.

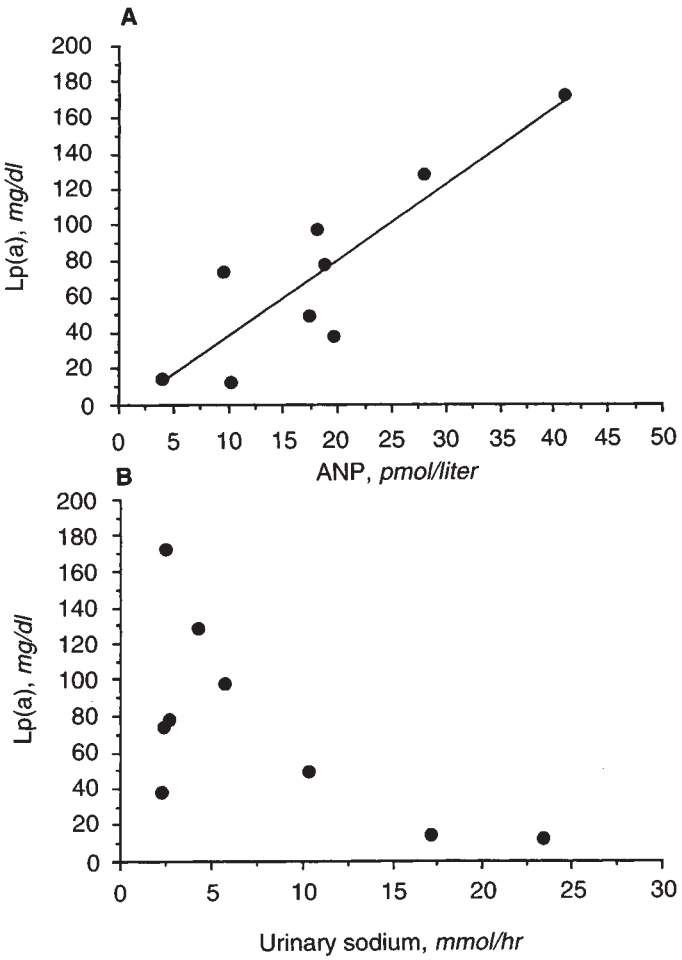

Fig. 5. *Correlations between plasma Lp(a) and plasma ANP* ($r = 0.88$; $P < 0.01$) *and hourly urinary sodium excretion* ($r = -0.67$; $P < 0.05$) *in 9 patients with nephrotic syndrome of fairly recent onset.*

patients with IgA nephropathy and ≈25% of the healthy controls (Fig. 1). The latter percentage may seem high for Caucasians, but it accords with recent studies reporting that about 25% of the Swedish population has Lp(a) levels above 30 mg/dl [33]. Hitherto, the genesis of the increased levels of plasma Lp(a) concentration in patients with NS has not been clarified. In the present study, no correlations between Lp(a) and parameters relating to the severity of the NS, such as serum albumin, UPE or GFR were found. This accords with findings in previous studies, such as those of Thomas et al who found no correlation between Lp(a) and serum albumin levels [17] and Karádi et al who found no correlation between the Lp(a) concentration and the degree of urinary protein loss [16].

Only a weak correlation was found between Lp(a) and serum cholesterol, and no correlation was found between Lp(a) and Apo B (Table 6). Indeed, an increase in Lp(a) is not an inevitable consequence of increased serum LDL-cholesterol concentrations, since primary hypercholesterolemias other than familial hypercholesterolemia are not conspicuously associated with raised Lp(a) values [34], and differing effects on LDL and Lp(a) have been found in the presence of growth hormone [35]. The underlying mechanism for both hyperlipidemia and increased Lp(a) levels may be multifactorial. In the present study, we found an excellent correlation between both VLDL-cholesterol and VLDL-triglycerides and Lp(a) levels, which may indicate that an increased hepatic synthesis causing the increase in both lipoproteins may be of importance (Fig. 2). It is well known that the availability of triglycerides is of major importance for hepatic lipoprotein secretion [36]. However, hypertriglyceridemia which is associated with increased VLDL production does not necessarily result in increases in plasma Lp(a) levels. It is therefore possible that the complex metabolic changes in the liver in nephrosis might affect the synthetic rate of both VLDL and Lp(a) [37]. Further studies are needed to evaluate these possibilities. At any rate, our findings demonstrate a close connection between triglyceride-rich lipoproteins (VLDL) and Lp(a) in nephrosis. Also under normal conditions, Lp(a) is to some extent associated with triglyceride-rich lipoproteins, and this fraction might be increased in nephrosis [38]. However, the removal rate of VLDL is greatly reduced in rats with experimentally induced NS, and defective clearance might therefore contribute to the high levels of VLDL and, possibly, Lp(a) [39]. The results of studies by Davies et al [39] indicate that in NS the defective clearance of chylomicrons and VLDL is caused by the urinary loss of macromolecules other than albumin. In this context, our finding of low orosomucoid levels (reflecting defective synthesis and/or substantial urinary losses) and a significant inverse correlation between orosomucoid and Lp(a) levels in NS patients is of interest. It has been observed that injection of α_1-acid glycoprotein (orosomucoid)

into nephrotic rats corrects the defect in the removal of triglyceride, which may indicate that orosomucoid is of importance for the lipid metabolism in NS [40]. Recently reported results of studies on rat muscle and glomerular capillaries indicate that orosomucoid is of vital importance for the maintenance of capillary permselectivity and that decreased levels of orosomucoid can be expected to result in an increased transcapillary passage of macromolecules [41, 42]. Interestingly, the deposition of Lp(a) in glomeruli has recently been documented in patients with glomerular disease and proteinuria [43]. In view of our finding of a significant inverse correlation between orosomucoid and Lp(a) levels, one could, albeit daringly, speculate that deficient orosomucoid levels may contribute to both elevation of circulating Lp(a) levels and perhaps also to an increase in vessel wall Lp(a). However, this question, of course, needs to be investigated further.

Our observation of significant decreases in plasma Lp(a) levels after remission of the NS indicates that Lp(a) metabolism undergoes profound changes during the remission process. This observation accords with the previous report of lower Lp(a) levels in eight patients with membranous nephropathy in remission, as compared to a different group of patients with membranous nephropathy and overt proteinuria [18]. Decreases in Lp(a) levels following treatment with prednisolone in patients with NS were reported by Takagoshi et al [19]. In the present study, we observed similar decreases in Lp(a) levels, irrespective of treatment with prednisolone, indicating that the fall in plasma levels of Lp(a) was the result of the correction of some factor(s) related to the nephrotic state *per se* rather than an effect of pharmacological treatment.

The plasma level of Lp(a) in the IgA nephropathy group with mild renal impairment and moderate, but non-nephrotic, proteinuria was not different from healthy controls, suggesting that proteinuria in the nephrotic range is essential for the development of high plasma Lp(a) levels in glomerular disease. An elevation of Lp(a) levels in advanced chronic renal disease has previously been described in patients treated with hemodialysis, peritoneal dialysis or diet [44, 45]. Moreover, high plasma levels of apo(a) in terminal renal failure patients have been reported to fall after renal transplantation [46]. All these observations indicate that advanced renal failure affects the regulation of Lp(a) metabolism. However, the cause of the elevated Lp(a) levels seen in chronic renal failure is not known. In the present study, no correlation between the degree of renal impairment and plasma Lp(a) levels was found, suggesting that moderate renal impairment, like that observed in our NS and IgA nephropathy patients, does not influence plasma Lp(a) levels *per se*. Other factors such as uremia, the presence or absence of nephrotic range proteinuria, other protein losses, genetic influence or other factors may be more important causes of elevations of plasma levels of Lp(a) in patients with chronic renal failure.

In conclusion, the present study confirms that patients with NS of diverse etiologies have markedly increased plasma level of Lp(a), in conjunction with other lipid abnormalities. In our study, the underlying renal pathology or GFR did not affect the prevailing plasma concentration of Lp(a). Plasma Lp(a) levels decreased substantially in all NS patients who experienced remission of the NS. In addition, the present study also demonstrates a relationship between VLDL and orosomucoid levels and the plasma levels of Lp(a) in NS.

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Appendix. Abbreviations

Lp(a) — Lipoprotein(a)
NS — Nephrotic syndrome
NS_{sg} — A subgroup of patients with nephrotic syndrome
C_{tot} — The total control group
C_{sg} — A subgroup of controls
UPE — Urinary protein excretion
ANP — Atrial natriuretic peptide
GN — Glomerulonephritis

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